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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 :
A61K 37/62

A1

(11) International Publication Number: WO 84/ 02274

(43) International Publication Date: 21 June 1984 (21.06.84)

(21) International Application Number: PCT/US83/01922

(22) International Filing Date: 7 December 1983 (07.12.83)

(31) Priority Application Number: 448,154

(32) Priority Date: 9 December 1982 (09.12.82)

(33) Priority Country: US

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(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: ACTIVATED, STABILIZED ENZYMES USEFUL FOR WOUND HEALING

(57) Abstract

Compositions containing a plurality of enzymes, starch, a plurality of amino acids and gland or organ extracts for treating fibrin associated disorders.

ACTIVATED, STABILIZED ENZYMES USEFUL FOR WOUND HEALING

BACKGROUND OF THE INVENTION

The term "wound" as used herein is intended to refer to the cellular disruption of mammalian tissue which is either traumatic, as in the case of a burn or cut, or, on the other hand, representative of a degenerative process, such as the gradual accumulation of arterial plaque, which may lead to thrombus formation and strokes. In either case, the sticky cell fragments called platelets are strongly implicated.

In the case of overtly traumatic wounds such as puncture wounds or bruises, platelets clump at the wound site, partially sealing the leak. The aggregated platelets activate the protease thrombin, which in turn acts to polymerize circulating plasma fibrinogen to form fibrin. Fibrin "hardens" by forming a series of peptide crosslinks to form the blood gel which becomes a clot.

The process of clot, or thrombus, formation on the interior of the blood vessels is less well understood. The normally smooth surfaces of the arterial walls become roughened and eroded in pre-thrombolytic conditions, possibly due to a circulatory overload of dietary fats such as lipoprotein-cholesterol crystals which accumulate as plaque on the arterial walls. As

blood flow slows down because of the obstruction, platelets begin to stick to the epithelial layer of the lumen. This platelet aggregation stimulates the formation of fibrin from fibrinogen as in the case of traumatic wounds, which may lead to thrombus formation, and the risk of embolism. Fibrin formation is also accompanied by an increase in proinflammatory prostaglandins and prostanoids, such as leukotrienes, which cause all the symptoms of inflammation. These include further platelet aggregation, smooth muscle contraction, and the migration of leukocytes which adhere to swollen vascular cells

Under normal homeostatic conditions, the human body maintains a natural cleaning and purging mechanism to help alleviate the formation of arterial plaques by destroying the fibrin network which dissolves the plaques or clots. In a healthy organism, plasmin acts on fibrin and the active peptides formed by fibrin digestion stimulate the biosynthesis of antiinflammatory prostaglandins which inhibit platelet aggregation, relax smooth muscle and increase vascular permeability to nutrients. Circulating lipolytic enzymes also help to dissolve or reduce the lipid component of plaque. This overall process may be termed "wound-healing".

It has been proposed that the proteolytic thiol-enzyme ("SH-enzyme") bromelain acts to selectively inhibit the biosynthesis of proinflammatory prostaglandins, such as the platelet aggregating thromboxanes. The use of bromelain is indicated since the endogenous proteases such as circulating plasmin, trypsin, chymotrypsin, and lipases are inhibited by trauma or exposure to excessive stress. Bromelain also acts on fibrinogen and fibrin to give products similar to those formed by plasmin and which stimulate the biosynthesis of antiinflammatory prostaglandins such as PGI_2. See S. J. Taussig, Med.

Hypth., 6, 99 (1980), and J. M. Miller et al., Exptl. Med. Surg., 22, 277 (1964). Similar activity has been reported for the structurally similar plant proteases, the SH-enzymes papain, ficin, and chymopapain B. See Li-Pen Ctiao et al., Biochem. Biophys. Res. Comm., 27, 100 (1967).

Lung and spleen extracts have also been reported to process fibrinolytic activity at neutral pH, an effect probably due to the presence in these extracts of Cathepsin B1, which is also properly classed as an SH-protease. See H. Keilova et al., FEBS Letters, 11, 287 (1970).

Other exogenously administered proteolytic enzymes such as trypsin and chymotrypsin or alpha-chymotrypsin have been reported to have a favorable influence on the inflammatory process in thromophlebitis. The most common explanation for the antiedema action of all the proteolytic enzymes is that they enhance the lysis of soft (unpolymerized or partially polymerized) fibrin present in inflamed tissue. See B. Seligman, Angiology, 20, 22 (1964), and I. Innerfield et al., J. Clin. Invest., 31, 1049 (1952).

Pancreatin and Pancrelipase are pancreatic extracts comprising amylase, lipase, and protease which are used to treat patients with cystic fibrosis and with pancreatic insufficiency. See Remington's Pharmaceutical Sciences, A. Ossol ed., Mack Pub., Boston, Mass. (16th ed. 1980), at ch. 53 for a general discussion of the proteolytic enzymes.

The full potential for the use of one or more proteolytic enzymes with or without the use of pancreas-associated digestive enzymes for the alleviation of wound inflammation and the promotion of

healing has not been heretofore realized. The individual enzymes are unstable in moist air and in the digestive tract, tending to hydrolyze (self-lyse). Enzyme mixtures become deactivated due to cross reactions and aggregation. Also, many of the proleolytic enzymes are not sufficiently activated to lyse "hardened" fibrin, which is the primary component implicated in persistent thromboembolic disorders.

It is therefore an object of the present invention to provide compositions whereby effective wound-healing amounts of proteolytic enzymes may be orally administered to a patient suffering from a fibrin-associated disorder.

It is another object of the present invention to provide compositions whereby proteolytic enzymes may be activated so as to lyse fibringen and fibrin at wound sites.

It is another object of the present invention to enhance the antiinflammatory activity of proteolytic enzymes.

It is yet another object of the present invention to protect circulatory smooth muscle from plaque formation.

It is another object of the present invention to enhance the ability of proteolytic enzymes to reduce scarring and erythma in traumatized tissue.

SUMMARY OF THE INVENTION

The above objects are achieved by the present invention which provides compositions comprising mixtures of immobilized proteolytic enzymes in combination with a mixture of amino acids, dipeptides, and buffers. The enzymes of the combination are selected from those

indicated as effective in wound healing, and the amino acids are selected from those indicated to aid the digestive tract enzyme absorption and for their ability to stimulate enzyme activation in the healing process. Immobilization of the enzymes prevents their self-deactivation in the digestive tract and allows them to reach the site of the wound in the active state. Buffering agents are optional to protect the enzymes from hydrolysis by gut acid, to correct digestive tract pH imbalance, and to aid in enzyme absorption. The dipeptides employed are those indicated to enhance fibrin reabsorption. Lyophilized raw gland or organ concentrates are also useful in this invention.

DETAILED DESCRIPTION OF THE INVENTION

The pathology of wound-processes involved in both overt traumatic wounds (cuts, bruises, etc.) and in thromboembolic-type wounds has been discussed hereinabove, along with the action of certain enzymes in the healing process. "Wound-healing" as discussed herein is also intended to include the amelioration and counteraction of deleterious systemic effects which are caused by or which contribute to the wound pathology. Such effects include, but are not limited to, those associated with pancreatic shock, acidosis, and other malfunction. These states may both contribute to thromboembolic pathology such as plaque and clot formation and may inhibit wound-healing processes. When pancreatic enzyme production is disrupted, the resultant inhibition of fat digestion and absorption reduces the cellular biosynthesis of prostaglandins which are essential to the maintenance of cell wall integrity. The inflammatory processes associated with thrombus formation also enhance the secretion of inflammatory prostaglandins, including those which are known to increase gastric acid secretion. The increased acidity

inhibits pancreatic excretion of digestive enzymes and tends to degrade enzyme supplements, thus slowing the wound-healing process.

The compositions of the present invention are formulated so as to deliver wound-healing amounts of proteolytic enzymes to the traumatized site in conjunction with amino acids and peptides which tend to aid the gut absorption of the wound-healing amino acids and to activate them at the wound site. The enzymes are substantially immobilized by delivering them in conjunction with a starch component so that they are efficiently absorbed in the presence of excess gut acid without being deactivated by self- or cross-lysis or hydrolysis. Buffering salts are also administered via the compositions of the present invention which tend to reduce or stabilize the acidity so as to aid reestablishment of the normal pancreatic function.

Supplemental pancreatic enzymes are also components of the present composition. These enzymes act to restore normal lipid metabolism in the small intestine so as to encourage the biosynthesis of antiinflammatory and platelet-declumping prostaglandins, and to assure adequate cell nutrition during the healing period.

As an essential component, the compositions of the present invention include two or more fibrolytic, proteolytic enzymes. Proteolytic enzymes generally function to hydrolyze or to lyse proteins into their component amino acids, thus providing these essential amino acids in nutritively-adequate ammunts. Fibrolytic enzymes have the added capability to lyse or digest fibrin clots at wound sites, thus restoring free blood flow through the circulatory system and speeding healing, i.e., clot dissolution, at traumatic wound sites. An especially useful class of proteolytic enzymes

is the thiol-enzymes, comprising papain, chymopapain, bromelain, cathepsin and ficin. These enzymes have been demonstrated to effectively lyse fibrin clots in vivo in a variety of pathological and surgical conditions. They apparently function by hydrolysing the amide bonds connecting arginine and glutamic acid residues on adjacent fibrin strands, thus depolymerizing the fibrin clots. These enzymes can be obtained on the pure form from commercial sources, or via established procedures. The cathepsin enzymes may also be incorporated into the compositions of the present invention in the form of lung, spleen or liver extracts which are available from Armour, Kankakee, Ill. A procedure for the preparation of lung and spleen extracts useful as a cathepsin source is described by U. Okamoto, et al., in Thrombos. Haemostas. (Stuttg.), 42, 729 (1979), the disclosure of which is incorporated by reference herein. Other useful organ extracts include brain, pancreas, duodenum, adrenal, pituitary, orchic, liver, heart, ovary and/or kidney extracts. Such extracts are commonly obtained from bovine sources. Preferably thiol-enzymes will make up 10-80% of the total enzyme component of the compositions of the present invention.

The compositions of the present invention will also include one or more of the proteolytic pancreatic enzymes trypsin, alpha-chymotrypsin and chymotrypsin. Trypsins generally act to reduce wound inflammation and edema and also speed healing by the debridement of necrotic wounds and by fibrinolysis. It is postulated that this activity is at least partially due to the inactivation of the normally inactive precursor of collagenase, an enzyme which acts to soften connective tissue. Therefore, it is believed that the chymotrypsin-containing compositions of the present invention will be useful for alleviation of the symptoms of the collagen-vascular diseases such as rheumatoid

arthritis, lupus, and other auto-immune disorders. The trypsins are preferably employed in the compositions of the present invention in an amount equal to about 0.1-10% by weight of the total enzymes present.

The compositions of the invention will also preferably incorporate an amount of pancreatin, or of the individual primary enzymes incorporated therein, or of mixtures of the individual enzymes with pancreatin. Pancreatin primarily contains amylase, protease and lipase; digestive enzymes which act to break down dietary starch, protein and fat, respectively. Since pancreatic deficiency or overload is implicated in many situations involving wounds, it is believed that a supplemental amount of pancreatin is a beneficial adjunct to the administration of the fibrinolytic and antiinflammatory enzymes. Pancreatin aids in the restoration of normal digestive processes, including the proper metabolism of fats, which is necessary for the achievement of effective plasma levels of anticlotting and antiinflammatory prostaglandins. Pancreatin and/or its component enzymes preferably comprise up to about 90% of the enzyme mixture of the present compositions, most preferably about 15 to about 85%.

The total weight percent of the enzymes employed in the compositions of the present invention may be varied over a wide range. For example, 20-80% by weight of the enzymes may preferably be employed.

The compositions of the present invention will also include an enzyme stabilizing and activating mixture of a plurality of amino acids and dipeptides. The amino acids act as natural buffers and balance the pH of the compositions of the present invention as they dissolve in the gastrointestinal tract, thus protecting them from excess gastric acid. Mixtures of essential and

nonessential amino acids have been found to be effective in the practice of the present invention. Preferably, the amino acid mixture will comprise those which have been implicated in the stimulation of the body's cellular immune response, such as l-arginine and l-lysine and their salts. Preferably, the amino acids are selected to substantially exclude those amino acids present in the thiol-enzymes included in the compositions, i.e., cystine, glycine, serine, tryptophan or alanine. Exclusion of these enzymatic amino acids from the present compositions is believed to facilitate the cellular uptake of the wound-healing thiol-enzymes at the wound site. Therefore, an especially preferred amino acid mixture for use in the compositions of the present invention is a mixture of approximately equal weights of l-arginine.HCl, l-lysine.HCl, dl-methionine, l-glutamic acid, l-leucine and glutathione. The amino acid mixtures useful in the compositions of the present invention will preferably comprise about 0.1-50%, most preferably 0.2-40% by weight of the compositions.

The compositions of the present invention will also include a minor but effective amount, preferably 0.001-5.0% of a dipeptide of such amino acids, e.g., l-arginine-l-glutamate. It is believed that this dimer activates the reactive site of the fibrinolytic enzymes described hereinabove, thus enhancing their ability to cleave linked fibrin chains and dissolve clots.

Oral, buccal, vaginal or anal administration of effective amounts of active enzymes such as the thiol-enzymes and trypsins used in the compositions of the present invention is inhibited by the extreme reactivity of the enzymes, including their tendency to cross-lyse each other, thus resulting in a loss of potency at the wound site. To overcome this disadvantage the compositions of the present invention will include an

amount of starch, preferably wheat or potato starch, effective to physically immobilize the enzymatic components of the compositions and thus inhibit their deactivation. It has been found that the immobilization can be accomplished by mixing the powdered enzymes and amino acids with from about 1 to about 50% by weight of starch based on the weight of the entire composition.

Buffers may be incorporated in the compositions of the present invention. The term "buffers" as employed herein includes organic and inorganic acids and acid salts, such as alkali metal carbonates, bicarbonates and phosphates, and also compounds which complex organic acids by the process of chelation and esterification.

Flavone-containing glycosides (bioflavinoids) may also be incorporated in the compositions of the invention. Preferred glycosides are rutin, melin, eldrin and the like, which act to restore the permeability and flexibility of traumatized capillary walls. These gycosides, when present, may comprise up to about 20% of the composition, and are preferred for compositions adapted for administration in aqueous solutions. Other useful flavinoids and flavinols are disclosed in A. M. Ambrose, et al., J. Nutr., 38, 305 (1949), the disclosure of which is incorporated herein by reference.

Preferred buffers include citric acid-citrate and calcium and sodium bicarbonate. It is believed that the buffers both interact with the amino acids to stabilize the enzymes used, counteract the effect of excessive digestive tract acid, and promote the establishment of beneficial intestinal flora. Buffers, when used to make up a portion of the present compositions, preferably comprise about 1-10 percent by weight.

Various biologically inactive adjuncts may optionally be incorporated into the compositions of the present invention to aid in their compounding, ingestion, tableting, etc. Such adjuvants may include binders, lubricants, food glazes, sugar syrups, colorings and flavorings, which may be applied in amounts and by methods according to established pharmaceutical practices.

When formulated as tablets, the compositions of the present invention will preferably be enterically coated with standard coating compositions so that they resist solution in gastric fluid but disintegrate in the intestine. For a discussion of enteric coating methods useful in the practice of the present invention, see Remington's Pharmaceutical Sciences at pages 1590-1591, the disclosure of which is incorporated herein by reference.

Therefore, a preferred powdered composition will be formulated so as to contain about 30-80% of enzymes of which about 10-70% will be thiol-enzymes, about 0.1-10% will be trypsins and about 15-85% will be pancreatin or its component enzymes. About 0.1-30% amino acids will be incorporated in the compositions, along with about 0.002-2% dipeptide, about 1-50% starch and about 0-10% of organic or inorganic buffers. The above weight percentages do not include the additional binders used in the tableting process.

To prepare the compositions of the present invention a dry mix of the powdered glandular extracts (thymus, spleen, or lung), the amino acids and the dimer is prepared in a ribbon-type mixer and then the enzymes are sequentially added with continuous spraying with an alcohol soluble refined glaze under conditions of low atmospheric humidity. After the mixing of the enzymes

and amino acids is complete, the mixture contains about 5-10% by weight of glaze solids. The spray is discontinued and the buffers and starch are added to the stirred powder to form the final composition. The composition may be packages or encapsulated at this point, for administration via an aqueous enema, douche or capsule suppository.

The powdered composition may be tableted, for example, into 1000 mg or 450 mg tablets by any of the commercially-available dry tablet presses. The resultant tablets may be enterically coated, and then further coated with refined food glaze, talc, dusting powder, sugar syrup and dye, according to standard practice.

The invention will further be described by reference to the following detailed examples.

EXAMPLE 1

In accord with the present invention, three compositions were prepared with the following ingredients.

Component	Weight (Kg)		
PART A	EX IA	EX IB	EX IC
Thymus Substance (Armour Chemical Co., Kankakee, Ill.)	1.5	3.9	0.06
Spleen Substance (Armour Chemical Co.)	1.5	3.9	0.06

l-Arginine-HCL	0.5	1.3	0.02
l-Lysine-HCL	0.5	1.3	0.02
dl-Methionine	0.5	1.3	0.02
l-Glutamic Acid	0.5	1.3	0.02
l-Leucine	0.5	1.3	0.02
Glutathione	0.5	1.3	0.02

Component	Weight (Kg)		
	EX IA	EX IB	EX IC
PART A			
l-Arginine-l-glutamate	0.5	1.3	0.02
PART B			
Pancreatin	5.7	31.2	250.00
Papain	7.3	16.6	45.00
Bromolain	5.8	15.0	-
Ficin	2.0	3.3	-
Trypsin	0.3	2.0	6.00
Chymotrypsin	0.7	0.3	12.00
Lipase/Prolase/Amylase (1:1:1 wt/wt)	-	10.0	-
Rutin	-	16.65	-
Mannitol (binder)	-	-	440.00
PART C			
Magnesium Stearate (lubricant)	1.5	1.5	-
Alginic Acid (binder)	1.5	1.5	-
Calcium Bicarbonate	1.5	1.5	-
Starch (Potato) (Wheat)	3.0	3.0	243.00
Dicalcium Phosphate (binder)	33.8	33.8	-

The compositions of Ex's IA and IB were formulated by dry mixing the ingredients of Part A under conditions of low humidity (less than 30%) and then sequentially adding the ingredients of Part B while lightly spraying 7.4 grams of a solution of 24.0 ml of refined food glaze

in 16.7 ml of isopropanol. The ingredients of Part C are then added with continued mixing. The powdered composition is then pressed into 333,000 450 mg tablets on a Stoke's BB-2 tablet press using a 7/16 inch punch. The composition of Ex IB is similarly punched into 400,000 450 mg tablets using a 3/8 inch punch. The tablets of Ex's IA and IB are then enterically coated and finish coated by sequentially applying to each batch a total of 8.0 l of food glaze, 6.0 kg of talc, 7.9 l of suspension coating solution, 3.7 kg of dusting powder, 2.0 l of sugar syrup and 2.2 kg of Opalux pink AS1408 dye in 3, 6, 25, 10, 2 and 1 coatings, respectively, to yield the final tablets.

The enteric coated tablet preferably comprises about 50-90% enzymes, about 2-15% starch (although greater amounts may be used as a tablet filler), about 5-15% amino acids, and about 3-15% gland or organ extracts, wherein the percentages are by weight based on the ingredients listed. The tablets may alsoccontain about 0.05-10% of a calcium or sodium acid salt buffer, although the fillers may also exhibit some buffering effect.

The composition of Ex IC was formulated as a powder by dry mixing the ingredients in the order listed, and then packaging the resultant powder in 1 g foil packets.

The resultant formulations, when ingrested orally (as in the case of the tablets), or when dissolved in water (as in the case of the powder) and administered as an enema or douche, will effectively deliver wound-healing amounts of enzymes to wound sites such as bruises, cuts, burns, arterial clots, arthritic sites and the like.

The invention has general applicability as a technique for preparing compositions comprising a mixture of enzymes in which the enzymes are inhibited from adverse interaction and provision is made for an appropriate environment and activation to facilitate maximum utilization of the enzymes. Combinations of conventionally-available enzymes are adaptable to the present invention, as are combinations of enzymes with other types of therapeutic agents. Thus in its broad aspects, this invention comprises a mixture of enzymes as the major active ingredient which is susceptible to potential adverse interactions, a stabilizing long-chain molecule having available active sites, such as hydroxyl sites on starch, and a plurality of amino acids (including those provided by raw organ concentrates) to create the proper environment and activation for the enzymes.

While specific embodiments of this invention have been described in the disclosure in detail, variations and modifications of these embodiments can be effected by one of skill in the art within the scope and spirit of the invention as described and claimed.

I CLAIM:

1. A stable enzyme composition adapted for oral administration comprising:

(a) a plurality of proteolytic enzymes in an amount effective to produce a fibrinolytic effect at a wound site;

(b) an amount of starch effective to immobilize said enzymes;

(c) a plurality of amino acids; and

(d) a raw gland or organ concentrate selected from the group consisting of thymus, spleen, brain, pancreas, duodenum, adrenal, pituitary, orchic, liver, lung, heart, ovary and kidney.

2. The composition of claim 1 wherein the proteolytic enzymes comprise one or more thiol-enzymes.

3. The composition of claim 2 wherein the thiol-enzymes are selected from the group consisting of papain, bromelain, ficin, chymopapain, cathepsin, or mixtures thereof.

4. The composition of claim 2 further comprising a pancreatic enzyme selected from the group consisting of trypsin, chymotrypsin and alpha-chymotrypsin.

5. The composition of claim 2 further comprising a digestive enzyme selected from the group consisting of lipase, prolase, amylase or mixtures thereof.

6. The composition of claim 1 wherein the starch is wheat or potato starch.

7. The composition of claim 1 wherein the amino acids are selected from the group consisting of one or more of the amino acids selected from the group consisting of l-arginine, l-lysine, dl-methionine, l-glutamic acid, l-leucine and glutathione.

8. The composition of claim 2 comprising cathepsin-containing thymus and spleen extracts.

9. The composition of claim 2 comprising pancreatin.

10. The composition of claim 1 further comprising an amount of a bioflavinoid sufficient to enhance capillary wall flexibility.

11. The composition of claim 10 wherein the bioflavinoid is rutin.

12. The composition of claim 1 comprising an amount of buffer effective to allow substantial digestive tract absorptioh of said composition.

13. The composition of claim 12 wherein the buffer comprises a calcium or sodium salt of citrate or bicarbonate.

14. The composition of claim 1 comprising an amount of l-arginine-l-glutamate effective to activate said enzymes toward fibrinolysis.

15. The composition of claim 1 wherein said gland or organ concentrate is a lyophilized bovine organ extract.

16. The composition of claim 1 wherein said gland or organ provides an effective amount of cathepsin and assists in the absorption and utilization of said enzymes upon ingestion.

17. The composition of claim 1 in the form of an enterically-coated tablet comprising: about 50-90% of enzymes, about 2-15% of starch, about 5-15% of amino acids, about 3-15% of gland or organ extract, and about 0.05-10% of buffer.

18. The method of treating digestive disorders which comprises administering the composition of claim 5.

19. The method of reducing edema and inflammation which comprises administering the compositions of claims 4 or 14.

20. The emthod of treating degenerative and autoimmune disorders which comprises administering the composition of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/01922

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC[3]

A61K 37/62 424/94

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/94

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

424/94+95
435/175+178

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	US, A, 3,297,480 Published 10 Janaury 1967 Matsuda	1-20
A	US, A, 3,395,222 Published 30 July 1968 Colescott	1-20
A	US, A, 3,501,567 Published 17 March 1970 Choay	1-20
A	US, A, 3,841,971 Published 15 October 1974 Messing	1-20
A	US, A, 4,307,081 Published 22 December 1981 Klein	1-20
A	US, A, 4,361,551 Published 30 November 1982 Galbraith	1-20

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
15 February 1984	08 MAR 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Sam Rosen